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Fingolimod for Multiple Sclerosis: Mechanism of Action, Clinical Outcomes, and Future Directions

Matthias Mehling · Ludwig Kappos · Tobias Derfuss

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Abstract The oral sphingosine 1-phosphate receptor (S1PR) modulator fingolimod functionally antagonizes S1PR hereby blocking lymphocyte egress from secondary lymphoid organs to the peripheral blood circulation. This results in a reduction in peripheral lymphocyte counts, including potentially encephalitogenic T cells. In patients with relapsing multiple sclerosis fingolimod has been shown to be an effective treatment. In phase 2 and phase 3 studies fingolimod-treated patients had reduced disease activity clinically and in MRI. Although severe infectious complications occurred in single cases treated with fingolimod, the frequency of overall infections was comparable in fingolimod-treated patients and controls. Overall, in clinical studies fingolimod was well tolerated and had a favorable safety profile. In follow-up studies with continuous fingolimod, treatment showed sustained efficacy while being well tolerated.

Keywords Multiple sclerosis · MS · Therapy · Fingolimod · FTY720 · T cell · TRANSFORMS · FREEDOMS

M. Mehling · L. Kappos (✉) · T. Derfuss
Department of Neurology and Department of Biomedicine,
University Hospital Basel,
Petersgraben 4,
CH-4031 Basel, Switzerland
e-mail: lkappos@uhbs.ch

M. Mehling
Immunobiology Laboratory, Department of Biomedicine and
Medical Outpatient Department, University Hospital Basel,
Basel, Switzerland

L. Kappos · T. Derfuss
Clinical Neuroimmunology Laboratory/Department of Biomedicine,
University Hospital Basel,
Basel, Switzerland

Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) accompanied by substantial neurodegenerative processes. The heterogeneous clinical disease course, radiologic, and pathologic findings hamper a full understanding of the complex interrelationship of inflammatory response and tissue damage in different subgroups and phases of the disease [1, 2]. In recent years however, the immunologic mechanisms underlying the disease have been better understood and, based on this, new therapeutic approaches have been developed. This widened the therapeutic options substantially. Oral immunomodulators might broaden the therapeutic armamentarium and potentially provide effective, more convenient, and more selective treatment options of the inflammatory but also the neurodegenerative components of the disease. Among them, oral fingolimod is the first member of a new class of immunomodulators that targets sphingosine receptors. The drug has shown clinical and MRI efficacy in clinical phase 2 and 3 trials of relapsing MS and is now registered for the treatment of relapsing remitting MS in many countries [3••, 4••, 5••].

Mechanism of Action

Immunologic Effects

Fingolimod (FTY720) is a sphingosine analogue and is phosphorylated by sphingosine kinase 1 and 2 as its natural counterpart [6, 7]. Sphingosine-1 phosphate (S1P) binds to G-protein-coupled S1P receptors. To date, five subtypes of S1P receptors ($S1P_{1–5}$) have been identified (Table 1) [8]. T cells, B cells, and natural killer (NK) cells mainly express

Table 1 Expression of S1P subtypes in lymphocytes, glial cell subs, and neurons

$S1P_1$	$S1P_2$	$S1P_3$	$S1P_4$	$S1P_5$
Lymphocytes	Astrocytes	Lymphocytes	Lymphocytes	Lymphocytes
Astrocytes	Microglia	Astrocytes		Astrocytes
Microglia		Microglia		Microglia
Oligodendrocytes		Oligodendrocytes		Oligodendrocytes

S1P sphingosine 1-phosphate.

$S1P_1$ and to a smaller extent $S1P_{3–5}$ (T cells), $S1P_3$ (B cells), and $S1P_5$ NK cells [9]. In the CNS, astrocytes express $S1P_{1–3}$ and $S1P_5$ [10], microglia cells express $S1P_{1–3}$ and $S1P_5$ [11, 12], and mature oligodendrocytes express $S1P_1$, $S1P_3$, and $S1P_5$ [9, 13, 14]. In immune cells that recirculate to secondary lymphoid organs (SLOs) such as lymph nodes, binding of S1P to $S1P_1$ mediates egress from SLOs [15]. Phosphorylated fingolimod binds as an analogue of S1P to the S1P receptors $S1P_1$, $S1P_3$, $S1P_4$, and $S1P_5$. Binding of phosphorylated fingolimod to $S1P_1$ on lymphocytes results in internalization and degradation of the receptor [16]. As a result, $S1P_1$-mediated egress of lymphocytes from SLOs to the periphery is blocked [17, 18]. Accordingly, inhibition of lymphocyte egress from SLOs by fingolimod pertains most likely also autoreactive T cells that mediate inflammation in MS lesions [19]. In fingolimod-treated patients with MS the percentages of CD4+ and CD8+ T lymphocytes are reduced [20]. Among them naïve T cells and central memory T cells (TCM) that recirculate to SLOs on a regular basis are predominantly reduced, whereas effector memory T cells (TEM) that do not recirculate on a regular basis to SLOs account for the majority of blood T lymphocytes in fingolimod-treated MS patients.

In recent years a T-cell subset characterized by the production of interleukin (IL)-17 has been demonstrated to play a central role in various models of human autoimmune such disease as experimental autoimmune encephalomyelitis, the animal model of MS [21–23]. In patients with MS the number of IL-17A mRNA-positive Th17 cells is elevated in peripheral blood and Th17 cells are enriched in the cerebrospinal fluid of patients with MS [22–24]. In MS lesions, Th17 cells are detected in high numbers and have an enhanced capacity to kill human neuronal cells when compared with control T cells [25, 26]. Blood CD4+ T cells with phenotypic and functional characteristics of Th17 cells are contained predominantly within the TCM subset, but are not found in TEM cells [27]. As a consequence, reduction of TCM by fingolimod treatment coincides with a major reduction of CD4+ Th17-like cells in blood. This finding was supported by the reduced expression of the Th17-specific transcription factor RORC2 and of barely detectable secretion of IL-17 by T cells of fingolimod-treated patients. Together these findings suggest that TEM and TEMRA cells are the predominant T-cell subtypes that remain in the peripheral blood of patients treated with fingolimod, and that egress from SLOs of naïve T cells, TCM, and Th17 cells are inhibited by fingolimod.

Besides T cells, numerous immune cells such as B cells, dendritic cells, and macrophages express sphingosine receptors [28]. Results from human studies and animal models indicate that functional antagonism of S1P inhibits also their egress from SLOs or migration into peripheral tissue [29–31], but this has not been reported with regard to fingolimod therapy in patients with MS. It was shown that the production of the proinflammatory cytokine IL-12p70 by blood-derived myeloid cells was inhibited [32]. In dendritic cells the production of the anti-inflammatory cytokine IL-10 was reduced, indicating together with the aforementioned reduction of IL-12 secretion additive anti-inflammatory effects.

CNS Effects of Fingolimod

In addition to its effects on lymphocytes, fingolimod has been reported to exert direct effects on CNS cells involved in the pathogenesis of MS such as astrocytes, oligodendrocytes, and microglia. Fingolimod and the phosphorylated active form (fingolimod-P) cross the blood–brain barrier and drug levels are found in steady-state conditions in higher concentrations in the brain parenchyma than in blood in treated animals [33]. In the CNS fingolimod colocalizes with myelin, presumably as a result of its lipophilic nature [34, 35]. In CNS tissue from patients with MS, mRNA levels of S1P receptors are upregulated in cells adjacent to MS lesions, and a strong increase in $S1P_{1\&3}$ expression on reactive astrocytes is found in active and chronic inactive MS lesions [36]. In rodents, progenitor and mature oligodendrocytes express $S1P_1$ and $S1P_5$ in vivo and in vitro [13].

Fingolimod induces modulation of S1P receptors on human oligodendrocyte progenitor cells (OPCs) and regulates differentiation of OPCs into oligodendrocytes [37–39]. In a system of lysolecithin-induced demyelination in organotypic cerebellar slice cultures fingolimod enhanced remyelination and process extension by OPCs and mature oligodendrocytes [40]. These effects were mediated primarily through $S1P_3$ and $S1P_5$. Fingolimod further rescued human mature myelin-producing oligodendrocytes from serum and glucose deprivation–induced apoptosis [41]. In astrocytes S1P and fingolimod augmented extracellular signal–regulated kinase (ERK), which mediates signaling for cell proliferation

[42]. In the presence of tumor necrosis factor-α, $S1P_1$ and $S1P_3$ are upregulated in primary cultures of human astrocytes and fingolimod reduced the secretion of proinflammatory cytokines in these cells. This indicates regulation of S1P expression in astrocytes under proinflammatory conditions and direct anti-inflammatory effects of fingolimod in astrocytes [36]. In contrast to human astrocytes, fingolimod reduces ERK phosphorylation in human microglia cells [32].

Taken together, these findings implicate that fingolimod treatment, in addition to its effects on the composition of peripheral blood T-cell subsets, also has direct effects on oligodendrocytes, astrocytes, and microglia. These direct or indirect neuroprotective effects could serve as an explanation for the reduced loss of brain volume observed in fingolimod-treated patients [4••].

Clinical Outcomes

Clinical efficacy and safety of fingolimod in relapsing MS have been evaluated in one phase 2 and two phase 3 studies and resulted in approval of the drug for relapsing MS in 2010 by the US Food and Drug Administration (FDA). In the phase 2 study, 281 patients with active relapsing MS—defined by at least two relapses during the previous 2 years or one relapse in the previous year or one gadolinium-enhancing (Gd+) lesion on MRI—and an Expanded Disability Status Scale (EDSS) of 0 to 6.0 were equally randomized to receive oral fingolimod 1.25 mg or 5 mg or placebo once daily [3••]. The primary end point was the cumulative number of Gd+ lesions per patient in monthly MRIs. Both dosages of fingolimod reduced the total number of Gd+ lesions compared with placebo significantly. Also, several secondary end points were met: 1) The proportion of patients who were free from Gd+ lesions was greater in both fingolimod groups. 2) The annualized relapse rate (ARR) was reduced by 53% to 55% in fingolimod-treated patients. 3) Significantly more fingolimod-treated patients (86%) remained relapse-free when compared with the placebo group (66%). After completion of the core study patients were offered to enter an open-label, active-drug extension study in which the previously placebo-treated patients were randomized to fingolimod. Also, this group showed a significant decrease in the number of Gd+ lesions and the ARR after initiation of treatment with fingolimod.

In an open-label extension study following the phase 2 core study the reduced number of Gd+ lesions, which was observed during the first 6 months of fingolimod treatment in the core study, was sustained after 24 and 36 months and the majority of patients remained free from Gd+ lesions or new T2 lesions [43, 44]. In line with this most patients remained free from relapses and EDSS scores were stable. During months 15 to 24, patients receiving fingolimod 5 mg were switched to fingolimod 1.25 mg, which was related to fewer side effects while being comparably efficacious. MRI and clinical outcomes demonstrated a continuous beneficial effect of fingolimod treatment and confirmed the 24-month findings of the extension study.

The results of the phase 2 study were confirmed in two phase 3 studies. The FREEDOMS (FTY720 Research Evaluation Effects of Daily Oral therapy in MS) study was placebo-controlled; the TRANSFORMS (Trial Assessing Injectable Interferon Versus FTY720 Oral in RRMS) study compared fingolimod to the established MS therapeutic interferon-β1a (IFN-β1a; intramuscular once weekly).

In the FREEDOMS study patients were randomized to receive oral fingolimod 0.5 mg, fingolimod 1.25 mg, or placebo once daily over 24 months [4••]. A total of 1272 patients with relapsing MS with an EDSS between 0 and 5.5 who had one relapse during the last year or two relapses during the previous 2 years were recruited for the study. Mean age of patients was 37 years. Approximately 60% were treatment-naïve, mean disease duration was 8 years, and the mean EDSS was 2.4. Compared with placebo, treatment with fingolimod reduced the ARR significantly (fingolimod 0.5 mg: 0.18; fingolimod 1.25 mg: 0.16; placebo 0.4), which corresponds to a relative risk reduction of 54% to 60%. Also, the time to confirmed disability progression after 3 and 6 months was prolonged significantly in both fingolimod groups. In addition, several secondary end points were favorable for fingolimod: Fingolimod treatment decreased the number of Gd+ lesions and the number of new or enlarged T2 lesions significantly. Increase of the volume of T1-hypointense lesions as a marker for tissue damage and whole-brain atrophy were also reduced by fingolimod.

In the TRANSFORMS study patients were randomized in a double-dummy design to oral fingolimod 0.5 mg, fingolimod 1.25 mg, or IFN-β1a intramuscularly once weekly [5••]. A total of 1292 patients with relapsing MS with an EDSS between 0 and 5.5 who had one relapse during the last year or two relapses during the previous 2 years were recruited for the study. Mean age was 36 years, and the majority of patients (~56%) had previous treatment for MS, mostly IFN-β or glatiramer acetate. Average disease duration was 7.4 years, and the patients had a mean EDSS of 2.2. In both fingolimod groups a significant reduction of the ARR compared with IFN-β1a was noted (fingolimod 0.5 mg: 0.16; fingolimod 1.25 mg: 0.2; IFN-β1a: 0.33). Corresponding to this the proportion of relapse-free patients was significantly higher in fingolimod-treated patients (fingolimod 0.5 mg: 82.6%; fingolimod 1.25 mg: 79.8%; IFN-β1a: 69.3%). Patients in the fingolimod groups also had less Gd+ lesions, a reduced number of new or enlarged T2 lesions, and less brain atrophy.

In an extension of the TRANSFORMS study patients who were treated with IFN-β1a in the core study were

randomly assigned to receive 0.5 mg or 1.25 mg of fingolimod, whereas the initially fingolimod-treated patients continued their treatment [45••]. Primary end points were the ARR, disability progression, and MRI outcomes. Patients receiving continuous fingolimod had unchanged benefits in the ARR. Patients who were switched from IFN-β1a to fingolimod showed a significant decrease of the ARR. Also, numbers of new or newly enlarging T2 lesions, Gd+ lesions, and the rate of brain volume decline were reduced. Compared with patients who had switched from IFN-β1a therapy to fingolimod, continuously fingolimod-treated patients had a significantly lower ARR and reduced inflammatory activity in brain MRI. Side effects shifted in patients who were switched to fingolimod to a profile that is known from other studies in fingolimod-treated patients with MS.

In all clinical studies fingolimod was well tolerated and had a favorable safety profile. Apart from the fingolimod 5-mg group, in the phase 2 study the frequency of adverse events in fingolimod-treated patients was comparable with controls. Therefore, patients treated with fingolimod 5 mg were switched to fingolimod 1.25 mg during months 15 to 24 of the phase 2 extension study [44]. The vast majority of adverse events were mild to moderate in all study groups. The most common serious adverse events in fingolimod-treated patients were transient bradycardia and atrioventricular block related to the first dose of the medication, MS relapses, and basal cell carcinoma. Macular edema occurred in 1% of the patients in the 1.25-mg group and 0.5% of the 0.5-mg group and resolved in most patients after discontinuation of fingolimod therapy. Other adverse events occurred in less than 1% of the study populations.

In all clinical studies the frequency of overall infections was comparable in fingolimod-treated patients and controls. Nasopharyngitis was the most frequent infection with no differences between patients treated with fingolimod 0.5 mg or 1.25 mg and controls. In the placebo-controlled phase 3 study, lower respiratory tract infections (including bronchitis and pneumonia) were more frequent in patients treated with fingolimod. Two deaths related to herpes virus infections occurred during the TRANSFORMS study. One patient developed primary disseminated varicella zoster infection after exposure to a child with chicken pox while under corticosteroid treatment. One patient developed lethal herpes simplex encephalitis, primarily treated with intravenous corticosteroids for suspected relapse of MS.

Besides lymphopenia, elevated alanine aminotransferase (ALAT) levels were common abnormal laboratory findings in all study groups, but were more frequent in patients treated with fingolimod. Up to 12.5% of patients had ALAT levels three times the upper limit of the normal range or more. In all patients liver enzyme abnormalities returned to normal after drug discontinuation.

After completing the core phase 3 studies, patients were offered to enter into open-label, uncontrolled active-drug extension phases. Patients previously treated with placebo or IFN-β1a were switched to fingolimod 0.5 mg or 1.25 mg, whereas the others continue their assigned dosages.

Currently, all patients from the phase 2 and the two phase 3 studies are monitored in a single extension study. Herein all patients were switched to fingolimod 0.5 mg. Patients are scheduled every third month for clinical and laboratory assessments. The study aims at compiling additional data on the long-term safety and tolerability of fingolimod therapy.

Future Directions

After introduction of fingolimod for the treatment of relapsing MS, a phase 4 clinical program aims to assess tolerability and safety of the drug when used in patients under non-study condition. In addition to the follow-up studies of the clinical studies, this will also help to assess long-term tolerability of fingolimod. In autumn 2011, results of two phase 3b studies of fingolimod in MS will be available. One study assessed the effect of fingolimod treatment on the induction of an antigen-specific immune response to influenza vaccination as a model for a newly induced immune response and on the induction of a recall immune response to tetanus booster vaccination. In a second phase 3b study, tolerability of initiation of fingolimod treatment without the currently required 6-hour observation period for cardiovascular monitoring after the first dose was assessed. Because the mode of action may also have direct neuroprotective effects, fingolimod is being evaluated in a phase 3 study in patients with primary progressive MS. Ongoing phase 2 studies are evaluating the clinical efficacy and safety of new compounds that are more specific for certain S1P receptors with the aim to further improve the efficacy/safety profile.

Conclusions

Oral fingolimod is the first member of the new class of $S1P_1$ modulators and has been approved by the FDA and European Medicines Agency for the treatment of relapsing MS. Two large phase 3 clinical trials showed a superior efficacy of fingolimod compared to both placebo and IFN-β1a intramuscularly. Fingolimod was well tolerated and safe. The overall incidence of infections, including severe and serious infections, was comparable between control groups and those receiving fingolimod 0.5 mg. However, a slightly increased incidence of lower respiratory tract and

lung infections (mainly bronchitis) was seen in fingolimod-treated patients. Follow-up studies will continue to assess the long-term tolerability and safety of fingolimod. The study addressing the effects of fingolimod in primary progressive MS will potentially help to better characterize the neuroprotective effect of fingolimod.

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